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Research Article

Adverse Reactions Due to Fluorescein during Retinal Angiography

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Abstract

Purpose: Fast sequence fluorescein angiography is a commonly diagnostic procedure employed in retinal pathology. We evaluate the safety of sodium fluorescein for use in fundus angiography.

Methods: A total of 14,455 fluorescein angiographies were performed in 11,260 patients. The adverse reactions after the procedure were registered. In patients with history of dye sensitivity or any other allergy, intradermal testing was performed.

Results: 8,826 patients underwent this test for the first time, and 2,434 patients had already undergone fluorescein angiography. An intradermal skin test for predicting an anaphylactoid reaction to i. v. injection of fluorescein solution was performed in 196 patients, with 12 positive reactions.

The incidence of adverse reactions to the fluorescein was 1.28% (186 patients) with a frequency rate (FR) of 1:78. There were 114 mild adverse reactions [nauseas in 52 cases (0.35%, FR 1:278), vomiting in 22 cases (0.15%, FR 1:657), vasovagal phenomena in 24 cases (0.16%, FR 1:602) and excessive sneezing in 16 cases (0.11%, FR 1:903)], 71 moderate adverse reactions [urticaria in 46 cases (0.31%, FR 1:314), rash in 18 cases (0.12%, FR 1:803), pyrexia in 5 cases (0.03%, FR 1:2,891), chest pain in one case (< 0.01%, FR 1:14,455) and low back pain in one case (< 0.01%, FR 1:14,455)] and just one severe adverse reaction [one case of bronchospasm].

Conclusion: Fluorescein angiography is a relatively safe diagnostic procedure. The percentage of adverse reactions was 1.28%, the most frequent reaction was nausea (0.35%). These results are consistent with previous studies.

INTRODUCTION

Adolf von Baeyer initially synthesized fluorescein dye in 1871 [1]. Novotny and Alvis introduced fluorescein angiography in clinical ophthalmology in 1960 [2]. Since that moment, the fluorescein angiography is one of the most commonly diagnostic procedures employed in ocular pathology. Sodium fluorescein ($C_{20}H_{10}O_5Na_2$) is an organic dye, has a molecular weight of 376 daltons, and is 80% bound to plasma albumin. The remaining 20% is seen during angiography. The dye absorbs light in the blue range of the visible spectrum, with absorption peaking at 490nm (blue) and it emits light at 530nm (yellow).

It is metabolized by the liver and excreted by the kidneys. Most dye is cleared with 24 hours and patients should be warned that their urine will appear orange during this time. The fast sequence retinal fluorescein angiography is considered a relatively safe diagnostic test, however several adverse reactions have been reported. These range from mild (nausea, vomiting, sneezing, pruritus, vasovagal phenomena, inadvertent arterial injection), moderate (urticaria, rash, syncope, pyrexia, nerve palsy, local tissue necroses, thrombophlebitis at the injection site, gastrointestinal distress) to severe (laryngeal edema, bronchospasm, angioneurotic edema, cardiac arrest, myocardial infarction, basilar artery ischemia and seizures) [3-5].

Previous studies reported that the most frequent adverse reactions are mild (0.73-14%), being nausea and vomiting the most common reactions. Moderate and severe reactions are infrequent (1%) [3,4,6]. Most of these studies are retrospective and we can find considered differences between the incidence of adverse reactions observed.

The exact mechanism of adverse reaction in fluorescein angiography is not clear. Proposed mechanisms described, generally fall into one of the following categories: 1) anaphylactoid reaction: histamine release in the absence of antigen-antibody reaction 2) anaphylactic reactions involving an immediate immune (IgE-mediated) hypersensitivity reaction, 3) vagal responses resulting in bradycardia and arterial hypotension 3) physical or psychological trauma, 4) direct pharmacologic toxic effect resulting vasospastic, 5) tachycardia and myocardial stress caused by anxiety-related medullary sympathetic discharge, 6) effect of contamination of the drug, 7) systemic effects of phenylephrine and other topical midriatics or any combination of the mentioned factors [5,7]. We present a prospective study, probably the largest survey of adverse reactions to intravenous fluorescein angiography in Europe, to determinate the incidence of adverse events to dye.

MATERIALS AND METHODS

After obtaining Local Research Ethics Committee approval from the Hospital del Sureste and written informed consent, we studied 11,260 patients undergoing to 14,455 retinal fluorescein angiographies between November 2001 and May 2008. Patients were excluded if they were < 18 years, were pregnant patients or patients in use of corticosteroids, immunosuppressive or antihistamine drugs therapy.

A preoperative evaluation was performed half an hour before the test by an anesthesiologist. It consisted of anamnesis, physical examination and angiographic procedure explanation. If the patient reported history of dye sensitivity or any other allergy (except seasonal allergy), intradermal testing was performed using 0.2 ml of sodium fluorescein 2% solution and a positive result was recorded for a persistent wheal of greater than 0.8 cm. The result was read at 20 minutes and 24 hours after intradermal injection, in case of positive reaction to the test, we advised against to perform the angiography.

Seventy-four patients were not allowed to undergo the angiogram: 20 patients denied the informed consent after explanation, 42 patients presented acute hypertension (>160/100 mmHg) and 12 patients were positives to the intradermal test.

The retinal angiography was performed using sodium fluoresceine 20% (Oculos Fluorescein, Novartis Laboratories, Ltd. , Spain) in a single 3 ml dose intravenously (i. v.), administered over 3 seconds, and the site of injection was a hand vein. The images were caught through a Topcon Retinal Camera® 50 EX, assisted by a digital program (Ophthalmic Image Management System).

We used the same classification as Yannuzziet al. [5] to define adverse reactions to fluorescein. The adverse reactions that occurred during and after the procedure were registered in a standardized form by the ophthalmologist, and immediately the patients were examinated and treated by the anesthesiologist.

Extravasation of dye and i. v. injection sore were excluded as adverse reactions for not being considered a systemic clinical reaction to the dye. Reactions that occurred up to 48 hours after fluorescein injection were not considered related to the test.

RESULTS

A total of 14,455 fluorescein angiographies were performed on 11,260 patients prospectively. The 78.38% of the patients (8,826) underwent this test for the first time, and 2,434 patients (21.61%) had already undergone fluorescein angiography.

The mean age was 55 ± 18 years. Of the total enrolled patients, 7,090 (62.96%) were female and 4,170 (37.03%) were male. An intradermal skin test for predicting an anaphylactoid reaction to i. v. injection of fluorescein solution was performed in 196 (1.74%) patients, those cases where an adverse reaction would be suspected due to the patient history, with only 12 positive reactions (6.12%).

The incidence of adverse reactions to the fluorescein was 1.28% (186 patients) with a frequency rate (FR) of 1:78. There were 114 (0.78%, FR 1:127) mild adverse reactions [nauseas in 52 cases (0.35%, FR 1:278), vomiting in 22 cases (0.15%, FR 1:657), vasovagal phenomena in 24 cases (0.16%, FR 1:602) and excessive sneezing in 16 cases (0.11%, FR 1:903)], 71 (0.49%, FR 1:204) moderate adverse reactions [urticaria in 46 cases (0.31%, FR 1:314), rash in 18 cases (0.12%, FR 1:803), pyrexia in 5 cases (0.03%, FR 1:2,891), chest pain in one case (< 0.01%, FR 1:14,455) and low back pain in one case (< 0.01%, FR 1:14,455) and just one (< 0.01%, FR 1:14,455) severe adverse reaction [one case of bronchospasm] (Table 1). The incidence proportion of adverse reactions was 1.39% (201 patients) with a frequency rate of 1:72, because 15 people presented more than one adverse reaction. Eight patients had urticaria and cutaneous rash, three patients had nausea and rash, and three patients had nausea and urticaria and in one patient occurred bronchospasm and urticaria.

All the patients that refered adverse reactions underwent fluorescein angiography for the first time. The patients with positive test were not allowed to undergo the procedure. None of the patients with negative test had an adverse reaction. All the reactions were observed within the first hour after the dye injection.

Table 1: Adverse reactions to fluorescein.

Adverse events	No of subjects (FR)
Mild	114 (1:127)
Nausea	52 (1:278)
Vomiting	22 (1:657)
Vasovagal phenomena	24 (1:602)
Sneezing	16 (1:903)
Moderate	71 (1:204)
Urticaria	46 (1:314)
Rash	18 (1: 803)
Pyrexia	5 (1:2891)
Chest pain	1 (1:14455)
Low back pain	1 (1:14455)
Severe	1 (1:14455)
Bronchospasm	1 (1:14455)
TOTAL	**186 (1:78)**

FR = Frequency rate

DISCUSSION

Intravenous fluorescein angiography is a commonly performed and important valuable diagnostic procedure. Many studies have estimated the frequency of adverse reactions after angiography, the last major survey of adverse reactions in the world was performed 23 years ago [5]. We reviewed the European series and we found one large survey performed by Lepriet al. [8] in Italy with 10,003 procedures assessed and other report performed by Karhunenet al. [6] in Finland with 9,909 cases assessed. Therefore we present the largest survey of adverse reactions to intravenous fluorescein angiography in Europe. However, other large studies from around the world were performed, as the very large cohort examined by Yannuzziet al. [5], with 221,781 angiograms reported in the year 1984 as the result of a national survey.

The great majority of patients with ocular pathology have been exposed to fluorescein, in topical form, during routine ocular inspection, but the report of adverse reactions is almost nonexistent. In case of oral administration of fluorescein, the frequency of adverse reactions range between 1%-2% [9-12] and in case of intravenous fluorescein it is between 3%-20%[3-6,13,14-16].In our study, we have obtained an incidence of adverse reactions to dye injection of 1.28% and an incidence proportion of 1.39%. It is a very low rate if we compare with the frequency obtained by other authors. There are not others Spanish reports about adverse reactions of fluorescein to compare with, so we think that this extremely low value it is due to the elevate rate of patients underwent this test twice of more times (21.61%). In addition, our study filtered most of the patients with high probability of fluorescein sensitivity or allergy, performing the intradermal test.

Mild reactions as nausea, vomiting or vasovagal disorders were the most common adverse reactions and occurred in 1:127 patients (0.78%). Others authors report frequencies between 0.73-14% [4,8,17,18,19]. The activation of chemical receptors in the emetic nervous center located in the area postrema, cause the vomiting through integration with vagal nerve or vestibular system [20].

Moderate reactions such as urticaria or rash were infrequent, and occurred in 1: 204 patients (0.49%). In other studies, they ranged from 0.4% to 1.2% [4,5,19,21].

The pathophysiology of these effects involves different mechanisms as we mentioned before, although the anaphylactoid reaction, characterized by independent IgE mechanisms and activation of mast cells, complement system and alterations in arachidonic acid metabolism, is the most probable action mechanism responsible for these phenomena. All the adverse reactions were observed in patients who had undergone this test for the first time, this fact reinforces the anaphylactoid reaction (not IgE-mediated) as the responsible action mechanism [22,23].

We found five cases of autolimited pyrexia, probably due to mild infection or pyrogen reaction.

One patient presented chest pain five minutes after the dye injection, although he related an atypical chest pain, we performed an electrocardiogram, measured CK-MB and Troponin T enzymes that resulted normal, ruling out an acute cardiac infarction.

Another patient related a low back pain after diagnostic procedure; the patient had history of type 2 diabetes with diabetic nephropathy. The pain eased partly after administration of dexketoprofen 50 mg i.v. , but we decided to send the patient to the hospital´s emergency room in order to rule out a renal vein thrombosis (the diagnosis was “inespecific low back pain” treated with non steroid anti-inflammatorydrugs).

Severe adverse reactions were very rare (one case of bronchospasm) as other authors reported. There were no deaths recorded, though it may occur very rarely. Yannuzzi et al. [5] observed one death for each 222,000 patients, but with several doubts about the direct relation with the angiography procedure [5,24,25]

The adverse reactions produced by the intravenous use of fluorescein could be prevented by using cutaneous tests. We performed the intradermal skin test in 196 patients and 6.12% of them resulted positive. The prick test with sodium fluorescein at 10% has been suggested as a useful test to prevent the dye adverse reactions and discards the false positives of the intradermal skin test.

A possible limitation of this study was not to include only patients who had undergone fluorescein angiography for the first time, as well as the use of intradermal testing instead of using the prick test for prospective diagnosis of anaphylactoid reactions to fluorescein. Another limitation when we compared to other study groups, was to use always the same kind of dye; fluorescein isn’t the same everywhere in the world. Some hospitals and practices buy ready-packaged vials from individual companies (there being differences between the companies as well), some institutions produce their own fluorescein in their hospital pharmacy which has an influence on the susceptibility to adverse reactions

We conclude that the retinal fluorescein angiography is a relatively safe diagnostic test. Our results, from one of the largest survey of adverse reactions to intravenous fluorescein are consistent with previous studies, and show a low cumulative incidence of 1.39% of adverse reactions. However, one should be prepared to handle acute anaphylaxis and the physician should be in place to manage potential serious adverse reactions.

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